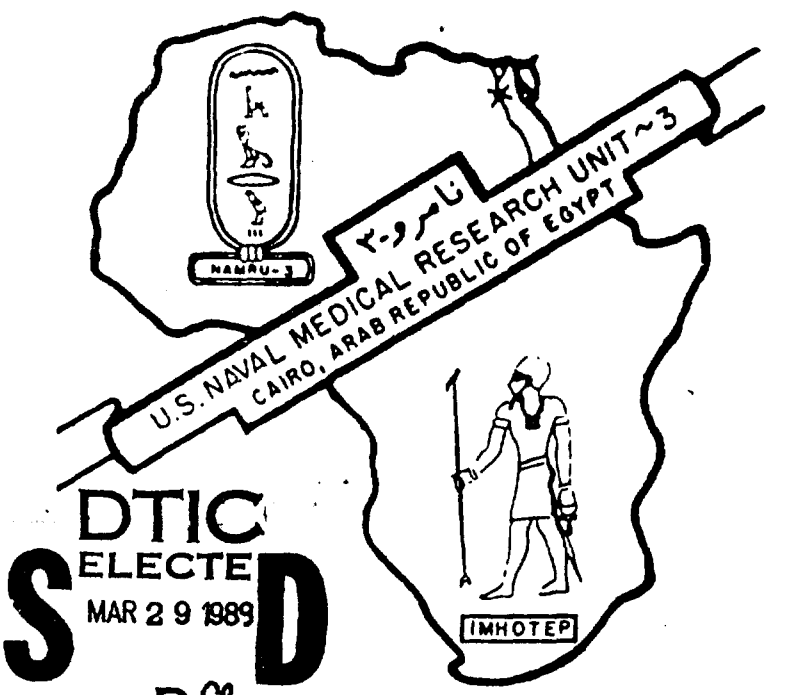
(2)



PUBLICATION REPORT

1513

32/88

EMPIRICAL TREATMENT OF SHIGELLA DYSENTERY WITH TRIMETHOPRIM: FIVE-DAY COURSE VS. SINGLE DOSE

BY

Edward C. Oldfield, III, August L. Bourgeois,
Abdul-Kadir M. Omar, and Gary L. Pazzaglia

U.S. NAVAL MEDICAL RESEARCH UNIT NO. 3
(CAIRO, ARAB REPUBLIC OF EGYPT)
FPO NEW YORK 09527

UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3 DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; Distribution is unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) 32/88	5 MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION U.S. Naval Medical Research Unit No.3 6b OFFICE SYMBOL (If applicable) NAVMEDRSCHU THREE	7a NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code) FPO New York 09527-1600	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION Naval Medical Research and Development Command 8b OFFICE SYMBOL (If applicable) NAVMEDRSCHDEV COM	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code) Naval Medical Command, National Capital Region Bethesda, MD 20814-5044	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO 64758A PROJECT NO 3M4647-58D849 TASK NO BH WORK UNIT ACCESSION NO DA301562

11. TITLE (Include Security Classification)
Empirical Treatment of Shigella Dysentery with Trimethoprim:Five-Day Course vs. Single Dose. (UNCLASSIFIED)

12. PERSONAL AUTHOR(S) Oldfield, Edward C. III, Bourgeois, August L., Omar, Abdul-Kadir M.*, and Pazzaglia, Gary L.

13a. TYPE OF REPORT	13b TIME COVERED FROM ____ TO ____	14. DATE OF REPORT (Year, Month, Day)	15 PAGE COUNT
		1987, June, 18	8

16 SUPPLEMENTARY NOTATION
Published in: Am. J. Trop. Med. Hyg., 37(3):616-623, 1987; Acc. No. 1513.

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Shigella Dysentery; Empirical Treatment; Trimethoprim; Patients.

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Fifty-three adults hospitalized with Shigella dysentery were empirically treated with trimethoprim (200mg) twice/day for 5 days, a single dose of trimethoprim (600mg), or placebo in a randomized double-blind trial. During the first 24 hr of therapy, there was a reduction in the number of stools in 18/21 (86%) of patients treated with the 5-day regimen (trimethoprim-5) and 13/15 (87%) of patients treated with a single dose (trimethoprim-1), compared with 7/17 (41%) of the placebo group ($P \leq 0.025$, both comparisons). The mean number of stools passed in the first 24 hr of therapy was 10.6, 10.8, and 21.3 stools in the trimethoprim-5, trimethoprim-1, and placebo groups, respectively. The mean (±SD) change in number of stools from baseline among treated patients during the first 24 hr was -4.9 (6.6) and -6.3 (6.3) for the trimethoprim-5 and trimethoprim-1 groups, respectively, compared with an increase of +2.4 (14.8) for the placebo group. There was a clinical failure at 48 hr in 9% of the trimethoprim-5 patients and 13% of trimethoprim-1 patients compared with 70% of placebo patients ($P < 0.005$, both comparisons). Although we were unable to demonstrate a difference in efficacy between

20 DISTRIBUTION/AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	21 ABSTRACT SECURITY CLASSIFICATION UNCLASSIFIED
22a NAME OF RESPONSIBLE INDIVIDUAL Research Publications Branch	22b TELEPHONE (Include Area Code) 20-2-820727 22c OFFICE SYMBOL R.P.B.

DD FORM 1473, 84 MAR 83 APR edition may be used until exhausted. All other editions are obsolete

SECURITY CLASSIFICATION OF THIS PAGE

★ U.S. Government Printing Office: 1986—607-044

UNCLASSIFIED

32/88 (Contd.)

19. the two dosage schedules of trimethoprim, we concluded that both treatment regimens are effective for the treatment of Shigella dysentery.

* Forlanini Fever Hospital, Ministry of Health, Mogadishu, Somalia.

Am. J. Trop. Med. Hyg., 37(3), 1987, pp. 616–623

EMPIRICAL TREATMENT OF *SHIGELLA* DYSENTERY WITH TRIMETHOPRIM: FIVE-DAY COURSE vs. SINGLE DOSE

EDWARD C. OLDFIELD III,* AUGUST L. BOURGEOIS,† ABDUL-KADIR M. OMAR,‡ AND GARY L. PAZZAGLIA*

*Departments of *Epidemiology and †Bacteriology, U.S. Naval Medical Research Unit No. 3, Cairo, Egypt, and ‡Forlanini Fever Hospital, Ministry of Health, Mogadishu, Somalia*

Abstract. Fifty-three adults hospitalized with *Shigella* dysentery were empirically treated with trimethoprim (200 mg) twice/day for 5 days, a single dose of trimethoprim (600 mg), or placebo in a randomized double-blind trial. During the first 24 hr of therapy, there was a reduction in the number of stools in 18/21 (86%) of patients treated with the 5-day regimen (trimethoprim-5) and 13/15 (87%) of patients treated with a single dose (trimethoprim-1), compared with 7/17 (41%) of the placebo group ($P < 0.025$, both comparisons). The mean number of stools passed in the first 24 hr of therapy was 10.6, 10.8, and 21.3 stools in the trimethoprim-5, trimethoprim-1, and placebo groups, respectively. The mean (±SD) change in number of stools from baseline among treated patients during the first 24 hr was −4.9 (6.6) and −6.3 (6.3) for the trimethoprim-5 and trimethoprim-1 groups, respectively, compared with an increase of +2.4 (14.8) for the placebo group. There was a clinical failure at 48 hr in 9% of the trimethoprim-5 patients and 13% of trimethoprim-1 patients compared with 70% of placebo patients ($P < 0.005$, both comparisons). Although we were unable to demonstrate a difference in efficacy between the two dosage schedules of trimethoprim, we conclude that both treatment regimens are effective for the treatment of *Shigella* dysentery.

The treatment of bacterial infections with single-dose antibiotic therapy offers many potential benefits. Studies of single-dose therapy for urinary tract infections have revealed less toxicity[1–3] and a decreased emergence of resistant strains.[4] Single-dose regimens also are less expensive, and because the entire regimen can be given under supervision, compliance approaches 100%. Single-dose therapy of shigellosis has previously been demonstrated to be effective, both clinically and bacteriologically, for tetracycline[5,6] and clinically for ampicillin.[7]

The treatment of shigellosis remains a problem because of increasing resistance to commonly prescribed drugs. Sulfonamides were the drug of choice in the 1940s; however, increasing resistance led to their replacement by tetracycline. Similarly, the development of widespread tetracycline resistance in the 1960s led to its replacement by ampicillin and, subsequently, to the replacement of ampicillin by trimethoprim-sulfamethoxazole in the 1970s.[8–10] The frequent occurrence of resistance to sulfamethoxazole[9,11,12] and the lack of synergy when the *Shigella* strain is resistant to sulfamethoxazole[11,13,14] suggests that the therapeutic effect of trimethoprim-sulfamethoxazole in many instances may be derived primarily from trimethoprim.

The efficacy of a 5-day course of trimethoprim in shigellosis has been previously demonstrated.[15] To evaluate the efficacy of a single dose of trimethoprim in *Shigella* dysentery, we conducted a randomized double-blind placebo controlled trial comparing the efficacy of trimethoprim single-dose (trimethoprim-1) to a 5-day regimen of trimethoprim (trimethoprim-5).

MATERIALS AND METHODS

All subjects (≥10 years old) with acute diarrhea seen at the Forlanini Infectious Disease Hospital in Mogadishu, Somalia, from April through June 1984 were admitted to the study.

Accepted 18 June 1987.

Address reprint requests to: Research Publications Division, NAMRU-3, FPO New York 09527-1600.

Diarrhea was defined as ≥4 stools in the preceding 24 hr with at least one associated symptom of nausea, vomiting, or abdominal pain. Patients who were pregnant, had known trimethoprim allergy, refused hospital admission, had diarrhea of >10 days duration, did not have *Shigella* isolated from stool, or had trimethoprim-resistant *Shigella* isolated from their stool were excluded from the study. All patients gave informed consent. All subjects had a baseline history and physical examination, which was repeated daily. Subjects gave a stool specimen prior to treatment and were randomly assigned to one of three groups. The trimethoprim-5 group received trimethoprim (200 mg) twice a day for 5 days, the trimethoprim-1 group received trimethoprim, 15 mg/kg or a maximum of 600 mg as a single dose, and the placebo group received an identical appearing placebo. Treatment was begun immediately after a stool was obtained for culture.

As the culture and antimicrobial susceptibility of *Shigella* isolates were determined (usually at 48 hr), each subject was evaluated without knowledge of the treatment regimen as to the need for antibiotic intervention. The code was broken for subjects who were clinically unchanged or worsening, or who had not had a reduction in stool number ≥50%. If the code was broken because of a lack of response, this was considered a treatment failure. Subjects in the placebo and trimethoprim-1 group were begun on trimethoprim, 200 mg, twice daily for 3 days, while those patients in the trimethoprim-5 group were continued on their regimen if the *Shigella* isolate was sensitive to trimethoprim. Clinical data was recorded blind.

Clinical scores were determined by giving 1 point for each of the following symptoms: fever, chills, headache, dizziness, nausea, vomiting, anorexia, myalgias, or malaise; 2 points for an oral temperature ≥100°F; 1 point for the presence of orthostatic blood pressure or pulse changes; and 1, 2, or 3 points for mild, moderate, or severe abdominal pain. Orthostatic changes were defined as an increase in pulse of ≥20 and/or a decrease in systolic blood pressure of ≥15 mmHg or a decrease in diastolic blood pressure of ≥5 mmHg after standing for 1 min. A clinical response was defined as a reduction in the clinical score of ≥50%.

Patients received oral rehydration salts and intravenous fluids according to the ward routine. A follow-up stool was obtained 5 days after initiation of therapy.

Microbiology

Stools were examined for bacterial and protozoal enteric pathogens before and after completion of treatment. Stools were plated at the patient's bedside onto MacConkey's (MAC), *Salmonella-Shigella* (SS), Hektoen enteric, and xylose-lysine-deoxycholate agars and into *Campylobacter* enrichment.[16] All stools were cultured on selective media for *Campylobacter* and *Yersinia*, and all plates were examined for *Aeromonas, Salmonella, Shigella, Plesiomonas, Vibrio*, and *Yersinia* using standard methods.[17–21] *Shigella* isolates were identified by slide agglutination in grouping and typing antisera (Difco, Detroit, Michigan) and biochemically with the API 20E system (Analytab Products, Plainsville, New York). Five pretreatment *Escherichia coli* colonies from bedside or laboratory MAC plates were assayed for enterotoxin activity.[22, 23]

Initial and post-treatment stools were examined for protozoal parasites microscopically by direct smear (wet mount). Stools, stained and preserved in merthiolate-iodine-formalin solution were reexamined for *Entamoeba* and *Giardia* at NAMRU-3 after ether extraction and centrifugation.[24] Direct fecal smears were also examined for red and white blood cells. The presence of fecal leukocytes was confirmed by examination of air-dried smears stained with Loeffler's methylene blue. After examining five fields, results were graded as follows: negative = <1 leukocyte/oil immersion field, 1+ = 1–5, 2+ = 6–10, 3+ = 11–20, and 4+ = 21+ leukocytes/field.

Quantitative stool cultures were performed on initial and post-treatment specimens to monitor trimethoprim-associated changes in the total number, species, and antibiotic susceptibility of resident aerobic gram-negative flora and to determine the relative number of *Shigella* present. Quantitative counts per gram of stool were done by serial dilutions onto MAC agar plates and incubated for 48 hr. For *Shigella* determinations, no detectable growth meant $<10^3$ organisms/g of stool, and was considered 10^2 in data analysis. Five colonies were selected from plates with the highest dilution showing growth and stored in nutrient agar stabs for later identification by API 20E and trimethoprim susceptibility testing.

Antibiotic susceptibilities to trimethoprim and other antibiotics were determined by disc diffusion.[25] Minimal inhibitory concentrations (MIC) of trimethoprim, sulfamethoxazole, and trimethoprim-sulfamethoxazole in combination (1:20) were determined by the agar dilution method with Mueller-Hinton agar (Mueller-Hinton II, BBL Microbiology Systems, Cockeysville, Maryland) and a Steers replicator.[27] *E. coli* (ATCC 25922) and *Staphylococcus aureus* (ATCC 25923) strains served as controls for both the disc diffusion and agar dilution procedures. The MIC of trimethoprim, sulfamethoxazole, and trimethoprim-sulfamethoxazole were determined for all strains of *Shigella*. Trimethoprim-susceptible strains were defined as those with MIC $\leq$ 4 μg/ml; sulfamethoxazole- and trimethoprim-sulfamethoxazole (1:20)-susceptible strains were defined as those with MIC $\leq$ 100 μg/ml, respectively.[28] Fractional inhibitory (FIC) indices < 1.0 were considered indicative of trimethoprim-sulfamethoxazole synergy[28, 29] and demonstrated that an individual *Shigella* isolate had enhanced susceptibility to the combined drugs at a ratio of 1:20.

Statistical analysis

The Kruskal-Wallis analysis of variance was used to test for differences among groups. Tests for differences between proportions were done using the χ^2 method with Yate's correction unless an expected cell frequency was <5. In these instances, Fisher's exact test was used. Spearman's ranking method was used for all correlation analyses.

RESULTS

A total of 53 patients met the criteria for study admission. There was no statistically significant difference between groups in regard to age, sex, weight, duration of diarrhea before treatment, pretreatment antibiotics, or number of stools in the 24 hr prior to study entry (Table 1) ($P > 0.05$ for all comparisons). All patients were moderately-to-severely ill with a mean number of stools of 18.9, 17.1, and 15.9 stools for the 24 hr prior to study admission for the placebo, trimethoprim-1, and trimethoprim-5 groups, respectively. Orthostatic changes were evident in 88.7% of patients, fever in 41.5%, fecal leukocytes were 3+ or 4+ in 94.2%, and visible blood was seen in the stools of 98.2%. There were no statistically significant differences in these variables between groups or in the mean number of *Shigella* per gram of stool (Table 2).

There were 29 exclusions. Twenty patients were excluded because their stool culture did not grow *Shigella*; three patients had a *Shigella* isolate resistant to trimethoprim; two patients were pregnant; two patients would not enter the hospital; one patient was not admitted because the hospital was full; and one patient left the hospital to be seen by a tribal healer and did not return.

All *Shigella* isolates, by study criteria, were sensitive to trimethoprim. Thirty-four of 54 (62.9%) isolates (one study admission was infected with two *Shigella* serotypes) were resistant to sulfamethoxazole (MIC >100 μg/ml), and 25 of 54 (46.3%) were resistant by disc diffusion (disc concentration = 300 μg). Synergy between trimethoprim and sulfamethoxazole was noted in all 20 *Shigella* strains that were sensitive to sulfamethoxazole by both MIC and disc diffusion, and in the 9 isolates with MIC >100 μg/ml but sensitive by disc diffusion. None of the 25 isolates resistant by both MIC and disc diffusion methods exhibited synergy.

Direct fecal smears and MIFs were negative for *G. lamblia* and *E. histolytica* trophozoites in all of the 52 specimens examined. In one patient in the trimethoprim-5 group and one patient in the trimethoprim-1 group an *E. coli* was isolated that produced heat stable (ST) enterotoxin. Although these patients had the longest and third longest time to last loose stool, both had clinical responses by 24 hr. Both heat stable-positive *E. coli* isolates were trimethoprim-sensitive by disc diffusion. No other enteric pathogens were isolated.

During the first 24 hr of therapy, 18/21 (86%) of the patients in the trimethoprim-5 group and 13/15 (87%) of the patients in the trimethoprim-1 group had a reduction in the number of stools relative to the 24 hr prior to therapy. Fewer patients in the placebo group (7/17) (41%) showed a reduction ($P < 0.011$ for both comparisons). The mean reduction in stool numbers during this period was 4.9 ($\pm$6.6) for the trimethoprim-5 group and 6.3 ($\pm$6.3) for the trimethoprim-1 group. In the placebo group, there was a mean increase in stool numbers of 2.4 ($\pm$14.8) ($P = 0.036$ for trimethoprim-1 vs. placebo, $P = 0.055$ for trimethoprim-5 vs. placebo).

During the first 24 hr of therapy, there were

TABLE 1

*Characteristics of 53 patients with shigellosis receiving placebo, trimethoprim single-dose, or trimethoprim five-day regimen**

Patient characteristics	Placebo (n = 17)	Trimethoprim	
		Single dose (n = 15)	Five day (n = 21)
Mean (±SD) age in years	3.2 (17.2)	36.5 (18.5)	33.2 (16)
Male : female ratio	1.0	2.0	0.9
Mean (±SD) weight in kg	49.0 (13.9)	52.1 (9.1)	48.0 (13.5)
Mean (±SD) duration of diarrhea before treatment, days	2.5 (1.4)	3.1 (2.3)	2.6 (1.4)
Mean (±SD) No. of stools in 24 hr before therapy	18.9 (8.4)	17.1 (8.1)	15.9 (8.7)
Percent self-treated with antibiotics prior to admission	82.4	60.0	85.7

* No significant differences between groups ($P > 0.05$ for all comparisons).

10.6 (±6.9), 10.8 (±8.7), and 21.3 (±13) stools passed in the trimethoprim-5, trimethoprim-1, and placebo groups, respectively ($P = 0.009$ for trimethoprim-5 vs. placebo, $P = 0.006$ for trimethoprim-1 vs. placebo). During the second 24 hr both treatment groups continued to show a reduction in number of stools passed compared with the placebo group (Table 3).

After 48 hr of therapy, 14/21 (66.7%), 10/15 (66.7%), and 4/17 (23.5%) in the trimethoprim-5, trimethoprim-1, and placebo groups, respectively, had shown a clinical response ($P = 0.020$ for trimethoprim-5 vs. placebo, $P = 0.036$ for trimethoprim-1 vs. placebo). Of the 4 patients in the placebo group who responded, 3 had quantitative *Shigella* counts of $<10^3$/g of stool. Conversely, 4/7 nonresponders in the trimethoprim-5 group and all nonresponders in the trimethoprim-1 group had *Shigella* counts $>10^5$/g of stool.

In the placebo group, 12/17 patients had the code broken at 48 hr and were treated with trimethoprim. This represents a 70% failure rate in the placebo group. In the trimethoprim-1 group the code was broken for 2/15 patients and in the trimethoprim-5 group in 2/21 patients, representing failure rates of 13% and 9%, respectively.

There were no significant differences between the trimethoprim-5 and trimethoprim-1 patients for any of the outcome variables, which included clinical response at 24 and 48 hr, number of stools or reduction in number of stools at 24 and 48 hr, time to last loose stool, or likelihood of a positive follow-up stool culture at 5 days after beginning treatment with trimethoprim.

The presence of fever prior to study entry was not associated with any outcome variable, whereas patients with orthostatic changes took longer to last loose stool in both treatment groups ($P = 0.05$, Spearman's rank).

The mean quantitative counts of *Shigella*/g of stool were 8.9×10^4, 4.8×10^5, and 6.1×10^4, respectively, for the placebo, trimethoprim-1, and trimethoprim-5 groups ($P > 0.25$). High log counts of *Shigella*/g of stool were associated with a decreasing likelihood of a positive clinical response at 48 hr ($P < 0.05$, Spearman's correlation) in the trimethoprim-1 and trimethoprim-5 groups. Among placebo patients, high *Shigella* counts were associated with a longer duration of illness before presentation, high numbers of stools passed in the 24 hr prior to study entry, and a poor clinical response at 24 hr ($P < 0.05$; Spearman's correlation).

TABLE 2

*Comparison of severity of illness at admission for three shigellosis treatment groups**

Number (percent) with clinical signs and symptoms	Placebo (n = 17)	Trimethoprim	
		Single dose (n = 15)	Five day (n = 21)
Orthostatic changes	15 (88.2)	13 (86.7)	19 (90.5)
Fever	7 (41.2)	6 (40.0)	8 (38.1)
Fecal leukocytes (>10/field)	15 (93.8)†	13 (92.9)†	21 (100.0)
Visible blood in stools	17 (100.0)	14 (93.3)	21 (100.0)
Shigella/g of stool (mean)	8.9×10^4	4.8×10^5	6.1×10^4

* No significant differences between groups ($P > 0.05$ for all comparisons).
† One missing observation.

TABLE 3
Comparison of clinical responses in three shigellosis treatment groups

Outcome variables	Placebo (n = 17)	Trimethoprim		P of difference vs. placebo	
		Single dose (n = 15)	Five day (n = 21)	Single dose	Five day
No. (%) of treatment failures*	12 (70)	2 (13)	2 (9)	<0.005	<0.001
No. (%) of patients with a reduction in stools at:					
24 hr	7 (41.2)	13 (86.7)	18 (85.7)	0.022	0.011
48 hr	10 (58.8)	14 (93.3)	20 (95.2)	0.030	0.009
Mean (±SD) No. of stools after beginning therapy:					
0–24 hr	21.3 (13.0)	10.8 (8.7)	10.6 (6.9)	0.006	0.009
25–48 hr	15.6 (13.0)	6.0 (4.9)	6.0 (7.1)	0.017	0.007
Mean reduction (±SD) in No. of stools during first 24 hr of treatment†	−2.4 (14.8)	6.3 (6.3)	4.9 (6.6)	0.036	0.055
No. (%) of patients with a positive clinical response at 48 hr	4 (23.5)	10 (66.7)	14 (66.7)	0.036	0.020

* Code broken at 48 hr.
† (n stools in 24 hr prior to treatment) (n stools in first 24 hr of treatment).

Prior to study entry, 77% of patients took antibiotics. Only 1 patient was self-treated with an antibiotic to which the subsequent *Shigella* isolate was susceptible. There was no significant difference between groups in the proportion of patients self-administering antibiotics ($P > 0.09$).

Follow-up cultures at 5 days after beginning therapy revealed a bacteriologic cure in 13/14 (92.9%) patients in the trimethoprim-1 group. In the one subject with a positive follow-up culture, the initial and follow-up isolates were sensitive to trimethoprim. In the trimethoprim-5 group, there were 14 negative follow-up examinations; in 4 cases a follow-up stool was not available. There were 3 bacteriologic failures at 5 days. Persistence of *Shigella* in the placebo group could only be evaluated in the 5 cases in which the code was not broken; 2/5 had positive cultures at 5 days. Relapses, defined as a recurrence of symptoms or diarrhea, occurred in 3/21 (14.3%) of the trimethoprim-5 and 0/15 (0%) of the trimethoprim-1 ($P = 0.18$). The relapses were of <24 hr duration and did not require retreatment in 2 of the 3 cases. There were no preliminary or outcome variables associated with likelihood of relapse in treated patients.

Side effects were minimal in all three groups. In the trimethoprim-5 group, 6 patients had symptoms felt to be related to therapy; 4 with headache, 1 with abdominal cramps, and 1 with dizziness. In the trimethoprim-1 group, there was 1 patient in whom headache may have been related to therapy. In the placebo group, there were 3 patients with headache, and 1 with nausea and malaise attributed to treatment.

DISCUSSION

Shigellosis remains one of the most common causes of diarrhea in the world today. It has been estimated that approximately 20% of patients with diarrhea worldwide who are admitted to a hospital have shigellosis.[30] An inexpensive, easily administered therapeutic regimen of low toxicity would be advantageous for the treatment of shigellosis. A single-dose regimen is less expensive than the standard 5 days of therapy and is easily administered with the ability to ensure essentially complete compliance. Studies of single-dose therapy for urinary tract infections also have revealed a decrease in toxicity as well as a decrease in the level of induced bacterial resistance when compared to conventional 7- to 10-day regimens.[1, 2, 4]

Previous studies of tetracycline have revealed that a 2.5 g single dose is effective in the treatment of shigellosis.[5, 6] However, this regimen may be associated with a significant amount of nausea and vomiting. Furthermore, many strains of *Shigella* are currently resistant to tetracycline (98% in the present study). Ampicillin has been shown to be clinically effective as a single dose (100 mg/kg) in the treatment of shigellosis, but a high incidence of bacteriologic failures has been noted

in both children and adults.[7] This is epidemiologically important as it allows continued spread of the disease. In addition, the high level of resistance to ampicillin (87% in the present study) makes this drug a poor choice for single-dose therapy.

Single-dose trimethoprim has not been adequately evaluated in the treatment of shigellosis. Consequently, we chose to conduct a randomized double-blind placebo controlled trial of trimethoprim. Trimethoprim was evaluated rather than trimethoprim-sulfamethoxazole, because an epidemiologic survey of this area in 1983 showed 81% of the *Shigella* strains were resistant to sulfamethoxazole, with no evidence of synergy with trimethoprim in the resistant strains. This lack of synergy between trimethoprim and sulfamethoxazole when the organism is highly resistant to sulfamethoxazole has been found by other studies[11, 13, 14, 31] and was reconfirmed in the present study; no synergy was noted in 25/25 *Shigella* strains resistant to sulfamethoxazole by both disc diffusion and agar dilution methods. In addition, a number of studies have revealed decreased toxicity with trimethoprim as compared to the combination of trimethoprim-sulfamethoxazole.[32, 33]

This study demonstrated that a single dose of trimethoprim is as effective as a standard 5-day course of trimethoprim in the treatment of shigellosis and that both regimens were superior to placebo. Both treatment regimens were superior to placebo in decreasing the number of stools passed in the first and second 24 hr after the institution of therapy, and in the number of clinical responses obtained at 48 hr (Table 3). In the placebo group the code was broken at 48 hr because of a lack of response in 70% of the patients, while in the two treatment groups the code was broken in only 11%. Comparing the trimethoprim-5 and trimethoprim-1 groups, there were no significant differences for any of the outcome variables (Table 3).

The common use of nonprescription antibiotics in Mogadishu was a concern as a possible source of bias in our results. In this study, 77% of the patients took antibiotics prior to study entry; however, there was no difference among study groups. Capsules of the commonly available antibiotics were shown to the patients and 43% identified tetracycline as the antibiotic they had taken. Most pretreated patients had taken only 2 or 3 capsules prior to study entry. One patient in the trimethoprim-5 group had taken 3 tablets of a sulfa drug the preceding day and had a *Shigella* cultured from his stool sensitive to sulfamethoxazole. This was the only patient who took an antibiotic prior to study entry to which the causative agent of his diarrhea was susceptible. Trimethoprim alone is not available, and trimethoprim-sulfamethoxazole is rarely used because it is 4–5 times more expensive than ampicillin, sulfa drugs, chloramphenicol, or tetracycline. The determination of quantitative *Shigella* counts was helpful in explaining some of the clinical inconsistencies: placebo responders and trimethoprim treatment failures. In the placebo group, 75% of those who had clinical responses had very low *Shigella* counts in their stools ($< 10^3$ *Shigella*/g of stool). These patients may have had either mild infections or were in the process of spontaneously clearing their infections. In contrast, 75% of the nonresponders in the trimethoprim treatment groups had *Shigella* counts $> 10^5$/g of stool.

In the present study, only 3 of 57 (5%) *Shigella* isolates were resistant to trimethoprim. However, we suspect, as with other antibiotics, that resistance to trimethoprim will develop as already has been documented in many areas of the world.[34] Ongoing monitoring of *Shigella* sensitivities should be conducted.

We conclude that a single dose of trimethoprim is as effective as a standard 5-day course of trimethoprim in the treatment of shigellosis, and that both regimens are superior to placebo. In areas of the world where the resistance of *Shigella* strains to sulfamethoxazole is high and only minimal synergy between trimethoprim and sulfamethoxazole can be expected, a single dose of trimethoprim would provide an inexpensive, minimally toxic, easily administered therapeutic regimen with virtually complete compliance for the treatment of shigellosis.

ACKNOWLEDGMENTS

We wish to thank Burroughs Wellcome Foundation for supplying the trimethoprim and placebo. A grateful acknowledgment is extended to David L. Call for his excellent technical assistance during all laboratory aspects of this study and to P. Echeverria (AFRIMS) and I. Mikhail (NAMRU-3) for kindly providing the enterotoxigenic *E. coli* and trimethoprim-sulfamethoxazole synergy results.

This study was supported by the Naval Medical Research and Development Command, NMC, NCR, work units 3M464758D849.-

BH.062 and 3M161102BS10.AA.421. The views of the authors do not purport to reflect those of the U.S. Navy Department.

REFERENCES

1. Tolkoff-Rubin, N. E., Weber, D., Fang, L. S. T., Kelly, M., Wilkinson, R., and Rubin, R. H., 1982. Trimethoprim-sulfamethoxazole for urinary tract infection in women. *Rev. Infect. Dis., 4:* 444–448.
2. Counts, G. W., Stamm, W. E., McKevitt, M., Running, K., Holmes, K. K., and Turck, M., 1982. Treatment of cystitis in women with a single dose of trimethoprim-sulfamethoxazole. *Rev. Infect. Dis., 4:* 484–490.
3. Souney, P., and Polk, B. F., 1982. Single-dose antimicrobial therapy for urinary tract infections in women. *Rev. Infect. Dis., 4:* 29–34.
4. Anderson, J. D., Aird, M. Y., Johnson, A. M., Ree, R., Goresky, D., Brumwell, C. A., and Percivall-Smith, R. K. L., 1979. The use of a single 1 g dose of amoxycillin for the treatment of acute urinary tract infections. *J. Antimicrob. Chemother., 5:* 481–483.
5. Pickering, L. K., DuPont, H. L., and Olarte, J., 1978. Single-dose tetracycline therapy for shigellosis in adults. *J. Am. Med. Assoc., 239:* 853–854.
6. Lionel, N. D. W., Abeyasekera, F. J. B., Samarasinghe, H. G., Goonewardena, C. V., and Tawil, G. S., 1969. A comparison of a single dose and a five-day course of tetracycline therapy in bacillary dysentery. *J. Trop. Med. Hyg., 72:* 170–172.
7. Gilman, R. H., Spira, W., Rabbani, H., Ahmed, W., Islam, A., and Rahaman, M. M., 1981. Single-dose ampicillin therapy for severe shigellosis in Bangladesh. *J. Infect. Dis., 143:* 164–169.
8. Barada, F. A., Jr., and Guerrant, R. L., 1980. Sulfamethoxazole-trimethoprim versus ampicillin in treatment of acute invasive diarrhea in adults. *Antimicrob. Agents Chemother., 17:* 961–964.
9. Nelson, J. D., Kusmiesz, H., Jackson, L. H., and Woodman, E., 1976. Trimethoprim-sulfamethoxazole therapy for shigellosis. *J. Am. Med. Assoc., 235:* 1239–1243.
10. Nelson, J. D., Kusmiesz, H., and Jackson, L. H., 1976. Comparison of trimethoprim-sulfamethoxazole and ampicillin therapy for shigellosis in ambulatory patients. *J. Peds., 89:* 491–493.
11. Hansson, H. B., Walder, M., and Juhlin, I., 1981. Susceptibility of shigellae to mecillinam, nalidixic acid, trimethoprim, and five other antimicrobial agents. *Antimicrob. Agents Chemother., 19:* 271–273.
12. Franzen, C., 1976. Experience of co-trimoxazole in the treatment of *Salmonella* and *Shigella* infections. *Scand. J. Infect. Dis., 8 (Suppl.):* 79–80.
13. Lewis, E. L., Anderson, J. D., and Lacey, R. W., 1974. A reappraisal of the antibacterial action of co-trimoxazole *in vitro*. *J. Clin. Pathol., 27:* 87–91.
14. Jarvis, K. J., and Scrimgeour, G., 1970. *In vitro* sensitivity of *Shigella sonnei* to trimethoprim and sulphamethoxazole. *J. Med. Microbiol., 3:* 554–557.
15. DuPont, H. L., Reeves, R. R., Galindo, E., Sullivan, P. S., Wood, L. V., and Mendiola, J. G., 1982. Treatment of travellers diarrhea with trimethoprim-sulfamethoxazole and with trimethoprim alone. *N. Engl. J. Med., 307:* 841–844.
16. Chan, F. T. H., and MacKenzie, A. M. R., 1982. Enrichment medium and control system for isolation of *Campylobacter fetus* subsp. *jejuni* from stools. *J. Clin. Microbiol., 15:* 12–13.
17. Blaser, M. J., Glass, R. I., Huq, M. I., Stoll, B. J., Kibriya, G. M., and Alim, A., 1980. Isolation of *Campylobacter fetus* subsp. *jejuni* from Bangladeshi children. *J. Clin. Microbiol., 12:* 744–747.
18. Schiemann, D. A., 1979. Synthesis of a selective agar medium for *Yersinia enterocolitica*. *Can. J. Microbiol., 25:* 1298–1304.
19. Martin, W. J., and Washington, J. A., 1980. Pages 195–219 *in* E. H. Lennette, A. Ballows, W. J. Hausler, and J. P. Truant, eds., *Manual of Clinical Microbiology*, Third edition. American Society for Microbiology, Washington, DC.
20. Von Graevenitz, A., 1980. *Aeromonas* and *Plesiomonas*. Pages 220–225 *in* E. H. Lennette, A. Ballows, W. J. Hausler, and J. P. Truant, eds., *Manual of Clinical Microbiology*, Third edition. American Society for Microbiology, Washington, DC.
21. Wachsmuth, I. K., Morris, G. K., and Feeley, J. C., 1980. *Vibrio*. Pages 226–234 *in* E. H. Lennette, A. Ballows, W. J. Hausler, and J. P. Truant, eds., *Manual of Clinical Microbiology*, Third edition. American Society for Microbiology, Washington, DC.
22. Sack, D. A., and Sack, R. B., 1975. A test for enterotoxigenic *Escherichia coli* using Y-1 adrenal cells in miniculture. *Infect. Immun., 11:* 334–336.
23. Dean, A. G., Ching, Y. C., Williams, R. G., and Harden, L. B., 1972. Test for *Escherichia coli* enterotoxin using infant mice: Application in a study of diarrhea in children in Honolulu. *J. Infect. Dis., 125:* 407–411.
24. Blagg, W., Schloegel, E. L., Mansour, N. S., and Khalaf, G. I., 1955. A new concentration technique for the demonstration of protozoa and helminth eggs in feces. *Am. J. Trop. Med. Hyg., 4:* 23–28.
25. Bauer, A. W., Kirby, W. M. M., Sherris, J. C., and Turck, M., 1966. Antibiotic susceptibility testing by a standardized single disk method. *Am. J. Clin. Pathol., 45:* 493–496.
26. Omitted.
27. Steers, E., Foltz, E. L., and Graves, B. S., 1959. An inocula replicating apparatus for routine testing of bacterial susceptibility to antibiotics. *Antibiot. Chemother., 9:* 307–311.

28. Washington II, J. A., 1981. Bactericidal tests. Pages 715–728 *in* J. A. Washington II, ed., *Laboratory Procedures in Clinical Microbiology*. Springer-Verlag, New York.
29. Busby, S. R. M., 1973. Trimethoprim-sulfamethoxazole. *In vitro* microbiological aspects. *J. Infect. Dis., 128 (Suppl.):* 442–464.
30. DuPont, H. L., and Pickering, L. K., 1980. *Infections of the Gastrointestinal Tract*. Plenum Publishing Corporation, New York, pp. 4–82.
31. Lexomboon, U., Mansuwan, P., Duangmani, C., Benjadol, P., and M'cMinn, M. T., 1972. Clinical evaluation of co-trimoxazole and furazolidone in treatment of shigellosis in children. *Br. J. Med., 3:* 23–26.
32. Neu, H. C., 1982. Trimethoprim alone for treatment of urinary tract infection. *Rev. Infect. Dis., 4:* 366–371.
33. Kasanen, A., and Sundquist, H., 1982. Trimethoprim alone in the treatment of urinary tract infections. Eight years of experience in Finland. *Rev. Infect. Dis., 4:* 358–365.
34. Murray, B. E., 1986. Resistance of *Shigella, Salmonella*, and other selected enteric pathogens to antimicrobial agents. *Rev. Infect. Dis., 8 (Suppl.):* 5172–5181.